

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Hours lying down per day, as a proxy for sedentary behaviour, and risk of diabetes in young and middle-aged adults in Norway: an 11-year follow-up of the HUNT Study
AUTHORS	Asante, Ernest O; Sun, Yi-Qian; Nilsen, Tom Ivar Lund; Åsvold, Bjørn Olav; Sørgerd, Elin; Mai, Xiao-Mei

VERSION 1 – REVIEW

REVIEWER	Guy Fagherazzi Luxembourg Institute of Health, Luxembourg
REVIEW RETURNED	20-Jan-2020

GENERAL COMMENTS	<p>The paper by Ernest et al. aims at evaluating the association between hours lying down and the risk of diabetes in a Norwegian cohort study.</p> <p>This is a legitimate research question given the rising health and societal issues related to the increase of sedentary behaviors.</p> <p>Major comments:</p> <ul style="list-style-type: none">- There is no clear definition of the type of diabetes. The definition of auto immune diabetes should be incorporated in the definition of the studied outcome in the material and methods section and not be presented only as a stratified analysis. Why no information from the clinical exam was used to specify the type of diabetes (type 1 or type 2 diabetes)? Why splitting in non-autoimmune diabetes vs auto-immune diabetes? What is the hypothesis with respect to hours lying down?- How do you disentangle the effect of hours lying down from sleep duration which is already known to be associated with the risk of type 2 diabetes?- Do you have information on total sleep duration per day? Can you adjust for it and study the hours lying down outside sleep?- I would avoid the term "modified" when referring to the interaction between hours lying down and physical activity. I would mention that there is an interaction and that the overall association is restricted to this subgroup- Is there an interaction with age?- Why not analyzing hours lying down as a continuous measurement, rather than losing information by analyzing categories? Consider using cubic spline regression models to derive the association between hours lying down and the risk for the outcome.- Patient and Public Involvement : how can the authors state that neither patients and members of the public were involved in such as a prospective cohort study including clinical examination?
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	Minor comments - Add the number of individuals and the follow-up in the title - Specify that hours lying down is used a proxy of sedentary behavior in the title and in the abstract - Specify the n of autoimmune and n of non autoimmune diabetes cases in the abstract
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Guy Fagherazzi

Institution and Country: Luxembourg Institute of Health, Luxembourg Please state any competing interests or state 'None declared': None declared

The paper by Ernest et al. aims at evaluating the association between hours lying down and the risk of diabetes in a Norwegian cohort study.

This is a legitimate research question given the rising health and societal issues related to the increase of sedentary behaviors.

Major comments:

- There is no clear definition of the type of diabetes. The definition of auto immune diabetes should be incorporated in the definition of the studied outcome in the material and methods section and not be presented only as a stratified analysis. Why no information from the clinical exam was used to specify the type of diabetes (type 1 or type 2 diabetes)? Why splitting in non-autoimmune diabetes vs autoimmune diabetes? What is the hypothesis with respect to hours lying down?

Reply: The definitions of autoimmune and non-autoimmune diabetes have been incorporated in the Methods section on page 7, and we there refer to a previous work in HUNT (Sorgjerd et al. ref. 19) explaining the rationale for these definitions in more detail. In brief, the measurement of serum glutamic acid decarboxylase antibodies (GADA) was used to clinically classify the types of diabetes into autoimmune diabetes when GADA ≥ 0.08 , nonautoimmune diabetes (called type 2 diabetes in the revised manuscript) when GADA < 0.08 and an unknown type due to lack of measurement on GADA. The numbers of types of diabetes have been updated in the Results on page 11 and in Table 2.

In accordance with the reviewer's comment, we have changed the term non-autoimmune diabetes to type 2 diabetes in the revised manuscript. However, we have kept the term autoimmune diabetes instead of type 1 diabetes, as in this adult study population a large proportion of the autoimmune diabetes cases are LADA (latent autoimmune diabetes in adults) rather than "classical" type 1 diabetes. Due to the relatively low number of participants with autoimmune diabetes (n=20), we did not have statistical power to perform separate analyses of LADA and "classical" type 1 diabetes.

We performed multinomial logistic regression analysis to evaluate if the associations were comparable for different types of diabetes. Due to few cases of autoimmune diabetes and the imprecise estimate, we are unable to conclude if prolonged hours lying down is associated with an increased risk of autoimmune diabetes. This has been acknowledged as a limitation in the discussion in the revised manuscript on page 18.

We hypothesized that longer hours of lying down per day were positively associated with the risk of diabetes. This has been added in the specific research objectives on page 5.

- How do you disentangle the effect of hours lying down from sleep duration which is already known to be associated with the risk of type 2 diabetes?

- Do you have information on total sleep duration per day? Can you adjust for it and study the hours lying down outside sleep?

Reply: Unfortunately, we do not have information on sleep duration specifically. This is a limitation of our study, which was mentioned in the Discussion section. Thus, we are unable to study the effect of hours lying down outside sleep time.

However, previous studies showed both short sleep and long sleep were associated with increased mortality and risk of diabetes. We did not observe that shorter hours lying down were associated with an increased risk of diabetes. Also, chronic diseases and depression are suggested to be associated with long sleep, and they further increase the risk of death. Our data showed that adjustment for chronic diseases in the main analysis and additional adjustment for sleep problems, and anxiety and depression symptoms in the sensitivity analysis did not change the observed association between prolonged hours lying down and risk of diabetes. All these suggested that our exposure variable was less likely to be a proxy for sleep duration. Please find the revised changes on page 18.

- I would avoid the term "modified" when referring to the interaction between hours lying down and physical activity. I would mention that there is an interaction and that the overall association is restricted to this subgroup

Reply: As interaction can also be presented as effect modification, we would like to keep the word "modified" at some places to simplify the phrasing. However, we have used term "interaction" at certain places following the reviewer's advice.

- Is there an interaction with age?

Reply: There was no interaction between categories of hours lying down and age as a continuous variable (p for interaction = 0.39) or age as a categorical variable ($p = 0.43$), possibly because we only included adults with an age range from 20 to 55 years.

- Why not analyzing hours lying down as a continuous measurement, rather than losing information by analyzing categories? Consider using cubic spline regression models to derive the association between hours lying down and the risk for the outcome.

Reply: The results generated from a cubic spline regression model are consistent with our results based on the categories of hours lying down (≤ 7 , 8 and ≥ 9 h/day). Both suggest that there is no association between shorter hours lying down and risk of diabetes. There seems to be a linear association beyond 8 hours lying down. Thus, it is inappropriate to treat the exposure variable as a continuous variable. In the revised manuscript we'd like to keep using the categories of hours lying down. The results from the cubic spline model are described in the results section on page 11 and are presented as a supplementary table (Table S4).

- Patient and Public Involvement: how can the authors state that neither patients and members of the public were involved in such as a prospective cohort study including clinical examination?

Reply: The statement has been changed to "There was no patient or public involvement in the design or data analysis of this study."

Minor comments

- Add the number of individuals and the follow-up in the title

Reply: The 11-year follow-up has now been added in the title. As the number of individuals in the original cohort differs from the number included in the analysis, we would like to specify the number in the abstract and methods where there is space for explanation.

- Specify that hours lying down is used a proxy of sedentary behavior in the title and in the abstract

Reply: "Hours lying down per day, as a proxy for sedentary behaviour" has been added in the title, abstract, study aim in the Background section and conclusions.

- Specify the n of autoimmune and n of non autoimmune diabetes cases in the abstract

Reply: Due to few cases and the imprecise OR for autoimmune diabetes, we are not able to conclude if prolonged hours lying down is associated with autoimmune diabetes. Therefore, we prefer not to highlight the results for subtypes of diabetes in the abstract of the revised manuscript.

The numbers of autoimmune and non-autoimmune diabetes (called type 2 diabetes in the revised manuscript) are given in the results section on page 11 and in Table 2.

VERSION 2 – REVIEW

REVIEWER	Guy Fagherazzi Luxembourg Institute of Health, Luxembourg
REVIEW RETURNED	24-Feb-2020
GENERAL COMMENTS	I thank the authors for taking into account most of my suggestions.